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Signed R. Mahoney

Dated 8 October 2003

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The Patent Office

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1. Your reference

45098.gb01/HRW

2. Patent application number
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0221480.7

16 SEP 2002

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

Laxdale Limited
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Patents ADP number *(if you know it)*

7482128001

If the applicant is a corporate body, give the

England & Wales

4. Title of the invention

Treatment of Anorexia Nervosa (AN) and Bulimia

5. Full name, address and postcode in the United Kingdom to which all correspondence relating to this form and translation should be sent

Reddie & Grose
16 Theobalds Road
LONDON
WC1X 8PL

91001

Patents ADP number *(if you know it)*

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application *(If you know it)*	Date of filing *(day/month/year)*

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing *(day/month/year)*

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a) any applicant named in part 3 is not an inventor, or
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Continuation sheets of this form	0
Description	8
Claim(s)	2
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Request for preliminary examination and search *(Patents Form 9/77)*	-
Request for substantive examination *(Patents Form 10/77)*	-
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11. I/We request the grant of a patent on the basis of this application.

Signature

Date
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12. Name and daytime telephone number of person to contact in the United Kingdom

H R WAKERLEY
020-7242 0901

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TREATMENT OF ANOREXIA NERVOSA (AN) AND BULIMIA

Anorexia nervosa (AN) is a severe illness which particularly effects adolescent girls and young women, but which can occur in both males and females of any age. There is a fear of weight gain, coupled with a pathological need to lose weight. Sufferers usually have a disturbed body image which means that they always perceive themselves as much heavier and fatter than they really are.

AN is becoming more and more common. AN sufferers often become strong advocates for the idea of weight control and do all they can to persuade others follow the same path. There are now large numbers of "PRO-ANA" web sites which promote AN and describe in great detail methods to enhance weight loss. These include, of course, strict dieting, methods of deceiving others about how much is being eaten, using diuretic drugs to promote water loss, using laxatives to provide diarrhoea, and using emetic drugs and other techniques to promote vomiting. In variants of the basic AN syndrome, some individuals eat relatively normally, or even binge eat large amounts, followed by vomiting and other extreme techniques to get rid of the food. This variant of AN is known as bulimia.

Although there are thousands of different theories, the root cause of AN remains unknown. No treatment has ever been found to be consistently successful. A recent detailed prospective study of available treatments found that there was no relationship between the type of treatment used and any long-term outcome (DI Ben-Tovim et al. Outcome in patients with eating disorders: A five-year study. Lancet, 2001; 357: 1254-

7). This means that no treatment is effective and probably also means that most of the theories on which treatments are based are wrong.

Those who do not know much about AN frequently underestimate its seriousness. In fact more than half of all patients never properly recover and have some form of lifelong eating disorder which seriously disrupts their lives. About 20% of sufferers will die, by far the highest death rate in any relatively common disease which affects young women, and which apparently starts in a way which is relatively benign, the need to diet.

New treatments are therefore urgently required. The present inventors claim a new treatment, the use of eicosapentaenoic acid (EPA) or one of its derivatives for the management of AN or related disorders such as bulimia. EPA is a highly unsaturated essential fatty acid which has been found useful in psychiatric and neurological disorders (EP 1148873 and EP 0956013). However, it has never, to the knowledge of the applicant, been proposed as a treatment for AN or bulimia. Indeed, in view of the unsatisfactory outcomes obtained when using psychiatric drugs for AN, there is no reason to believe on the basis of prior art that AN might respond to EPA.

The present invention provides a method of treating anorexia nervosa, bulimia and related clinical syndromes by administering to a subject eicosapentaenoic acid (EPA) in any appropriate form which can be assimilated by the body. The subject may one showing symptoms of, or believed to be at risk from AN or a related syndrome. The present invention also provides use of eicosapentaenoic acid (EPA) in any appropriate form which can be assimilated by the body in the manufacture of a medicament for the treatment of anorexia nervosa, bulimia and related clinical syndromes.

Eicosapentaenoic acid (EPA) can be administered in many different forms. The abbreviation "EPA" is used herein to refer to the acid, or its derivative, which is used in the preparations employed in the present invention. Thus the forms of EPA used in the present invention include the free acid, salts such as those of sodium, potassium, lithium or any other appropriate salt, mono-, di-, or triglycerides, phospholipids of various sorts, amides, esters including ethyl, methyl or other esters, and any other derivative which is biologically compatible and which can be demonstrated by standard assay techniques to raise the level of EPA in the blood of the patient. Combinations may be used. Preferred are the triglyceride or ethyl ester, the ethyl ester being particularly preferred.

EPA can be synthesised but with great difficulty because of its thirty-two isomers, only one of which involves all the double bonds in the cis configuration and which is biologically active. It is usually therefore prepared from natural EPA-containing sources including micro algae and other micro-organisms, a wide range of different marine oils from fish, shellfish and marine mammals and, increasingly, from genetically modified micro-organisms or higher plants. EPA from any of these sources may be used in the invention. These provide sources of the acid and its derivatives.

The EPA may be used in the form of the natural oils or preferably in partially purified or fully purified extracts or semi-synthetic derivatives containing preferably more than 70% of the pure compound (the free acid and/or its derivatives) and very preferably more than 90% or more than 95% of the pure compound. Pure EPA-triglyceride or the pure ethyl ester of EPA are particularly suitable for these purposes. It is increasingly evident

that EPA binds to highly specific sites in cells and that the binding can be interfered with by other fatty acids which can thus interfere with the activity of the EPA itself (DF Horrobin, Progr Drug Res, 2002). The best therapeutic results will therefore be obtained when the final pharmaceutical dosage form contains less than 10% in total and less than 3% individually of other fatty acids which might interfere with the action of EPA. Preferably the final dosage form should contain less than 5% in total and less than 2% individually of other fatty acids which might interfere with the action of EPA. The fatty acid of most concern in this context is the related fatty acid docosahexaenoic acid (DHA). Other fatty acids to be taken into consideration in this calculation are linoleic acid (LA) and arachidonic acid (AA). Preferably, the EPA contains less than 10% in aggregate and less than 3% individually of docosahexaenoic acid, linoleic acid and arachidonic acid. Still preferably, the EPA contains less than 5% in aggregate and less than 2% individually of docosahexaenoic acid and linoleic acid. It may also be preferred that there is less than 2% arachidonic acid in the EPA. EPA preparations of 1% or less DHA, LA or AA may be used. Alternatively, an EPA preparation in which DHA is substantially absent may be employed. In addition, the preparation may be substantially free from LA or AA, or both LA and AA.

The total dose of EPA to be used daily in the treatment of AN and related conditions may range from 50mg to 20g per day but will usually be in the range of 100mg to 5g/day and particularly in the range 300mg to 3g/day.

The usual route of administration will be in a pharmaceutical dosage form of capsules or micro-capsules or other appropriate form prepared by those skilled in the art. Other appropriate formats, particularly for AN patients, are:

1. Any form of liquid or emulsion or related dosage form for oral administration.

2. Any form of preparation for parenteral administration by intramuscular or intravenous routes which may be needed to bypass the food phobias seen with AN patients.

3. The addition of EPA at the appropriate dose to specialist medical foods which are specifically used for the treatment of AN patients, particularly liquid foods for oral administration or for administration by enteral tube feeding. EPA may also be added to nutritional supplements for patient with AN or related disorders, to be administered intravenously.

Example

A 15-year-old patient presented with a 14-month history of dieting and eating difficulties. These had started with dietary restrictions and excessive exercise and proceeded to laxative abuse. Two months prior to being first seen she had stopped taking all solid food. When first seen her weight was still within the normal range for her height at 55kg for 1.63m. However, she had lost 8kg since stopped solid food, had stopped menstruation and begun to grow the fine, downy "lanugo" hair over her body which is common in AN.

She was treated with a standard AN regime of family therapy, psychotherapy and dietary advice. This was ineffective and over the next two months she lost around 10kg which necessitated her admission to hospital. At this point she was extremely distressed and

unable or unwilling to maintain a conversation. Despite her emaciation she was still preoccupied with being fat and wanted to lose more weight. Her heart rate was very slow and her blood glucose was low, signs of starvation. She was treated as an emergency with compulsory naso-gastric feeding with parental consent. After two weeks of this therapy she had gained a little over 2kg and begun to eat small amounts by mouth. At the end of this time her family removed her from hospital against medical advice.

Over the following ten days she lost a further 5kg in weight to 42kg. Her doctors believed that her life was in danger and so obtained an order for compulsory admission to hospital. At the start of this admission she was treated with 1g/d of ethyl-eicosapentaenoate. This transformed her response to treatment. Over the following weeks she began to eat normally and within 12 weeks she was back to 57kg. Her mood and cognitive functions improved and she became normally communicative. Instead of being obsessed by weight and food to the exclusion of everything else, she became interested in all aspects of her life and her future. She lost her distorted body image perceptions and became confident about her appearance. After 12 weeks she was discharged from hospital and her body weight stabilised around a normal 62-65kg. She took a summer job which she enjoyed and completed successfully and enrolled in a college course. The changes with time are summarised in table 1.

This dramatic response to treatment demonstrates an entirely novel and unexpected approach to the management of AN and related eating and vomiting disorders. We therefore claim the use of EPA in any appropriate dosage form for the management of these disorders. Since patients with AN often suffer from general micronutrient deficiencies it is appropriate to combine the EPA with micronutrient supplements either

provided separately or in the same dosage form. Appropriate dosage forms include pharmaceutical unit dosage, nutritional supplements and specialist foods, including foods for administration by naso-gastric tubes or other enteral or parenteral routes.

Table 1. Changes in the status of a patient with AN treated with ethyl-EPA. The Morgan-Russell (MR) Outcome Scale is a well-recognised scale for assessing the status of patients with AN. The overall scale (MR-O) addresses the whole picture, while sub-scales address issues like food intake (MR-A), mental state (MR-C) and overall social-economic-health state (MR-E). The overall scale and its sub-scales are all scored from 0 to 12 where 0 indicates a severe problem and 12 indicates completely normal.

Event	Wt kg	MR-O	MR-A	Mr-C	MR-E
Pre-illness	63	12.0	12.0	12.0	12.0
1st doctor visit	55	1.9	2.7	4.0	1.0
1st hospital admission	45	1.9	2.7	4.0	0.0
1st hospital discharge	47	1.0	0.0	4.0	0.0
2nd hospital admission	42	1.2	0.0	4.0	1.0
2nd hospital discharge on EPA	57	12.0	12.0	8.0	9.0
3 months after discharge	63	12.0	12.0	12.0	11.0

Claims

1. A method of treating anorexia nervosa, bulimia and related clinical syndromes by administering eicosapentaenoic acid (EPA) in any appropriate form which can be assimilated by the body.

2. Use of eicosapentaenoic acid (EPA) in any appropriate form which can be assimilated by the body in the manufacture of a medicament for the treatment of anorexia nervosa, bulimia and related clinical syndromes.

3. A method according to claim 1 or use according to claim 2, in which the EPA is from a natural EPA-containing oil.

4. A method according to claim 1 or use according to claim 2, in which the EPA is in the form of the free acid, an appropriate salt, a mono-, di-, or triglyceride, a phospholipid, an amide, an ester or any other biologically compatible derivative.

5. A method according to claim 1 or use according to claim 2, in which the EPA is in the form of the triglyceride or the ethyl ester.

6. A method or use according to claim 1, 2, 4 or 5, in which the EPA is more than 70%, preferably more than 90% and very preferably more than 95% pure.

7. A method or use according to claim 6, in which the EPA contains less than 10% in aggregate and less than 3% individually of docosahexaenoic acid, linoleic acid and arachidonic acid.

8. A method or use according to claim 6, in which the EPA contains less than 5% in aggregate and less than 2% individually of docosahexaenoic acid and linoleic acid.

9. A method or use according to claims 7 or 8, in which the EPA is in the form of the ethyl ester.

10. A method or use according to any preceding claim, in which the EPA is for oral administration in an appropriate pharmaceutical dosage form and is given at a dose between 50mg and 20g/d, preferably between 100mg and 5g/day and very preferably between 300mg and 3g/day.

11. A method or use according to any preceding claim, in which the EPA is for parenteral, intramuscular or intravenous administration in an appropriate pharmaceutical dosage form.

12. A method or use according to any of claims 1 to 10 wherein the EPA is added to a nutritional supplement for patient with AN or related disorders, such supplement to be taken orally, or given by enteral tube, or given intravenously.